

# Pharmaceutical Supply Chain Security

Updated October 31, 2013

Congressional Research Service

<https://crsreports.congress.gov>

R43106

## Summary

The drug package that a community pharmacist hands to a patient, or a hospital pharmacist sends to a patient's bedside, or a physician administers in the medical office has reached the end of a complicated path. That path is called a supply or distribution chain. The upstream portion of the chain includes the journey of each active and inactive ingredient and their chemical components to the manufacturer that creates the finished drug product. The downstream chain, which this report addresses, includes the repackagers, wholesale distributors, associated storage and transport companies, and, finally, the dispenser. Dispensers include independent community or chain pharmacies, hospitals or other health care facilities, and physicians' offices.

Usually the supply chain provides consumers with unadulterated prescription drugs. However, the chain is potentially vulnerable, and when it breaks, a dispenser might provide a counterfeit product containing no active ingredient, less-than-labeled dosage, or a dangerous substitution. The dispenser might also provide a mishandled or diverted drug that has become sub- or superpotent or has gone past its expiration date. In addition to the potential harm to patients, these security breaches can affect a manufacturer's reputation and financial bottom line.

Congress has addressed pharmaceutical supply chain security several times over the past 107 years. The 1906 Food and Drugs Act focused on labeling; the 1938 Federal Food, Drug, and Cosmetics Act (FFDCA) addressed adulteration, misbranding, and the registration and inspection of manufacturing establishments; and the Prescription Drug Marketing Act (PDMA, P.L. 100-293) required that wholesale distributors be licensed by the states and required that a wholesale distributor, except one in a specified ongoing relationship with the manufacturer, provide to the purchasing distributor or dispenser a statement—called a pedigree—“identifying each prior sale, purchase, or trade of such drug.” More recently, the Food and Drug Administration Amendments Act of 2007 (FDAAA, P.L. 110-85) required the Secretary to “develop standards and identify and validate effective technologies for the purpose of securing the drug supply chain against counterfeit, diverted, subpotent, substandard, adulterated, misbranded, or expired drugs”; and, in 2012, the Food and Drug Administration Safety and Innovation Act (FDASIA, P.L. 112-144) expanded registration and reporting requirements. Despite current federal law and actions by state legislatures, opportunities for breaches of the supply chain continue to exist. The 112<sup>th</sup> and 113<sup>th</sup> Congresses have worked to craft a set of national requirements that would protect both patient and manufacturer, and allow the assignment of accountability for identified problems, while attempting to manage cost and avoiding a confusing patchwork of state legislation.

In their work, House and Senate policymakers have been considering many decisions. These include, for example, definitions; pedigrees; track-and-trace technologies; serialization; lot- and unit-level requirements; authentication; interoperable data collection and systems; data confidentiality and access; requirements for transaction reporting and notification regarding suspect deliveries; implementation timing; licensure, registration, and accreditation standards for entities in the supply chain; accountability; cost; and the relationship between federal and state laws. After passing individual bills (H.R. 1919 and S. 959), majority and minority leadership of the House Committee on Energy and Commerce and the Senate Committee on Health, Education, Labor, and Pensions announced an agreement on September 25, 2013. The House passed the text of the agreement, H.R. 3204, on September 28, 2013, and the bill awaits Senate action.

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## Pharmaceutical Supply Chain: Why People Care

The prescription drug that you picked up on the way to work this morning may have changed hands many times before the pharmacy clerk handed you the amber vial with its sticker label and perhaps one or two multi-page information inserts about the drug. That means that there were many potential opportunities for your drug to be mishandled or even substituted with a counterfeit. The counterfeit could be a watered down version of the actual drug, a sugar-filled non-medicinal fake, or a substitute chemical that looks, weighs, and reacts like the real drug but is actually toxic. While, overall, the U.S. drug supply is typically safe, Congress, the Food and Drug Administration (FDA), industry groups, and consumers are working to devise a system to limit opportunities for counterfeiting and mishandling.

Health experts call the drug's journey a *supply chain*. It begins with the ingredients a manufacturer uses, carries through the manufacturing process, and continues through the distribution system of wholesalers, warehouses, and transportation to the dispensing retail and institutional pharmacies—all the way to you, the consumer, the patient.<sup>1</sup> FDA, a federal scientific regulatory agency within the Department of Health and Human Services (HHS), regulates not only which drugs manufacturers may sell in the United States but also the integrity of the drugs through the supply chain, which is now global.<sup>2</sup>

In April 2013 testimony before the House Committee on Energy and Commerce, Janet Woodcock, the Director of FDA's Center for Drug Evaluation and Research, described the chain as follows.<sup>3</sup>

[T]he increasingly complex drug supply chain, from raw source materials to finished products for consumers, presents multiple opportunities for the product to be contaminated, diverted, or otherwise adulterated. Our efforts to secure the supply chain include minimizing risks that arise anywhere along the supply chain continuum, from sourcing a product's ingredients through the overseeing of a product's manufacture, storage, transit, sale, and distribution. A breach at any point in this continuum could lead to dangerous and even deadly outcomes for patients.

Dr. Woodcock referred to problems “including contamination, diversion, counterfeiting, and other adulteration.”<sup>4</sup> She gave several examples of counterfeit and stolen or diverted products: counterfeit Adderall and Vicodin sold on the Internet; stolen insulin vials needing refrigeration that were later purchased by patients without accountability for appropriate handling; and a stolen and expired seizure drug that “made it back into the legitimate supply chain and was being returned for credit.”<sup>5</sup>

<sup>1</sup> Because the term *consumer* could refer to retail or hospital pharmacy or clinician's practice that purchases the drug from a distributor or the manufacturer in addition to the person who uses the drug, this report uses the term *patient* to refer to the person who uses the drug.

<sup>2</sup> Statement of Deborah M. Autor, Deputy Commissioner for Global Regulatory Operations and Policy, Food and Drug Administration, Department of Health and Human Services, before the Committee on Health, Education, Labor, and Pensions, United States Senate, September 14, 2011, <http://www.fda.gov/NewsEvents/Testimony/ucm271073.htm>.

<sup>3</sup> Statement of Janet Woodcock, Director, Center for Drug Evaluation and Research, Food and Drug Administration, Department of Health and Human Services, before the Subcommittee on Health, Committee on Energy and Commerce, U.S. House of Representatives, hearing on “Securing Our Nation's Prescription Drug Supply Chain,” April 25, 2013, <http://www.fda.gov/NewsEvents/Testimony/ucm349186.htm>.

<sup>4</sup> *Ibid.*

<sup>5</sup> *Ibid.*

Additional examples of specific breaks in the supply chain include human growth hormone bought from Medicaid patients and sold by a Florida wholesaler in 2008;<sup>6</sup> insulin cargo stolen in 2009 that appeared among drugs sold by three wholesalers;<sup>7</sup> and, in 2010, a licensed Texas wholesaler offering prescription drugs obtained from patients.<sup>8</sup> Other publicized breaches of the supply chain have involved “fraudulent versions” of Botox “sold by unlicensed suppliers who are not part of the legitimate U.S. supply chain”;<sup>9</sup> counterfeit Lipitor that U.S. consumers purchased from United Kingdom sources;<sup>10</sup> and counterfeit Avastin (with no active ingredient) that some U.S. medical practices bought from foreign distributors.<sup>11</sup>

This report serves as a primer on pharmaceutical supply chain issues.<sup>12</sup> It (1) describes the chain from manufacturer<sup>13</sup> to patient, including where it is vulnerable; (2) summarizes current federal law, regulation, and FDA policies that Congress and the agency designed to protect the integrity of the final drug product, and indicates where those protections may falter; (3) notes state-level and professional association activities; and (4) discusses areas that Congress, FDA, and industry, health care, and patient stakeholders have suggested might be changed to increase the security of the pharmaceutical supply chain.

## Pharmaceutical Supply Chain: How It Works

To understand how the supply chain functions, it helps to know the extent of FDA’s involvement with prescription drug safety and effectiveness. FDA regulates the approval, production, distribution, and advertising of prescription drugs.<sup>14</sup> It works to prevent unsafe, ineffective,

<sup>6</sup> FDA Office of Criminal Investigations, link to Department of Justice June 4, 2009 press release, <http://www.fda.gov/ICECI/CriminalInvestigations/ucm277094.htm>.

<sup>7</sup> Statement of Deborah M. Autor, Deputy Commissioner for Global Regulatory Operations and Policy, Food and Drug Administration, Department of Health and Human Services, before the Committee on Health, Education, Labor, and Pensions, United States Senate, September 14, 2011, <http://www.fda.gov/NewsEvents/Testimony/ucm271073.htm>; and FDA, “Update to FDA Alert About Stolen Insulin,” August 26, 2009, <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm180320.htm>.

<sup>8</sup> FDA Office of Criminal Investigations, link to Department of Justice March 18, 2010 press release, <http://www.fda.gov/ICECI/CriminalInvestigations/ucm271770.htm>.

<sup>9</sup> FDA, “Fraudulent Versions of Botox Found in the United States,” Drug Safety and Availability, April 26, 2013, <http://www.fda.gov/Drugs/DrugSafety/ucm349503.htm>.

<sup>10</sup> FDA, “Counterfeit ‘Lipitor’ Sold in the United Kingdom,” Safety Alerts for Human Medical Products, August 2, 2005, <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm151056.htm>.

<sup>11</sup> FDA, “Counterfeit Version of Avastin in U.S. Distribution,” Drug Alerts and Statements, February 14, 2012, <http://www.fda.gov/Drugs/DrugSafety/ucm291960.htm>.

<sup>12</sup> Other sources that provide background information include FDA, “FDA Counterfeit Drug Task Force Reports,” <http://www.fda.gov/Drugs/DrugSafety/ucm169825.htm>; Government Accountability Office (GAO), “Food and Drug Administration: Response to Heparin Contamination Helped Protect Public Health; Controls That Were Needed for Working With External Entities Were Recently Added,” GAO-11-95, October 29, 2010; Pew Health Group, “After Heparin: Protecting Consumers from the Risks of Substandard and Counterfeit Drugs,” July 12, 2011, [http://prescriptionproject.org/after\\_heparin\\_report/](http://prescriptionproject.org/after_heparin_report/); Institute of Medicine (IOM), *Countering the Problem of Falsified and Substandard Drugs*, Gillian J. Buckley and Lawrence O. Gostin, editors, Washington DC: National Academies Press, 2013;

<sup>13</sup> This report focuses on the downstream supply chain—from the manufacturer to the consumer. The upstream supply chain involves the paths of the active and inactive ingredients and their processing that occur before the manufacturer creates the finished product.

<sup>14</sup> FDA also regulates the safety and effectiveness of animal drugs. This report addresses only the human drug supply chain.

subpotent, superpotent, or adulterated drugs from reaching pharmacies and patients in the United States—whether introduced on purpose or inadvertently.<sup>15</sup>

*Before FDA approves* a manufacturer’s application to sell a prescription drug, it requires, among other things, that a manufacturer demonstrate that its product is safe and effective for its intended use, that directions on the label are clear and appropriate, and that the drug will be manufactured in specific production lines that have been registered and approved by FDA. *After FDA approves* the application, the manufacturer must continue production according to FDA-approved “good manufacturing practices” (GMPs).<sup>16</sup> The manufacturer must register each establishment involved in drug production with FDA and provide a list of current products,<sup>17</sup> and periodically open its production facilities to FDA inspection.

After production, the manufacturer typically sends, perhaps via a repackager, the drug to FDA-registered U.S. drug wholesale distributors (authorized distributors of record, secondary wholesale distributors, and others) for further distribution. Industry observers estimate that “consumers receive 11 million prescriptions per day from more than 150,000 locations throughout the US. Our drug distribution network involves tens of thousands of independent companies.”<sup>18</sup> States license or authorize the pharmacists and wholesalers who sell and distribute pharmaceuticals within their borders and also license the physicians and dentists who prescribe the drugs.

As illustrated in **Figure 1**, many entities are part of the downstream pharmaceutical supply chain. Definitions of the players vary somewhat across federal and state laws and regulations and across proposed federal systems.<sup>19</sup> The following textbox provides general descriptions.

<sup>15</sup> For a fuller discussion, see CRS Report R41983, *How FDA Approves Drugs and Regulates Their Safety and Effectiveness*, by Susan Thaul.

<sup>16</sup> See, for example, FDA, “Current Good Manufacturing Practices (cGMP) for Drugs: Reports, Guidances and Additional Information,” Page Last Updated: 10/07/2010, <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnsweronCurrentGoodManufacturingPracticescGMPforDrugs/default.htm>; FDA, “Questions and Answers on Current Good Manufacturing Practices (CGMP) for Drugs,” Page Last Updated: 12/20/2012, <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm124740.htm>.

<sup>17</sup> FDA, “Drug Registration and Listing System (DRLS & eDRLS),” Page Last Updated: 04/12/2013, <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/DrugRegistrationandListing/ucm2007058.htm>.

<sup>18</sup> Adam Fein, “Securing America’s Pharmaceutical Supply Chain,” Drug Channels blog, May 15, 2008, <http://www.drugchannels.net/2008/05/my-op-ed-securing-supply-chain.html>, printed in Pharmlot blog, May 13, 2008, <http://www.pharmlot.com/2008/05/the-op-ed-securing-the-supply-chain/>.

<sup>19</sup> FDA, “The Prescription Drug Marketing Act: Report to Congress,” 2001, [http://www.globalcompliance.com/pdf/Prescription%20Drug%20Marketing%20Act%20\(PDMA\)%20Report%20to%20Congress.pdf](http://www.globalcompliance.com/pdf/Prescription%20Drug%20Marketing%20Act%20(PDMA)%20Report%20to%20Congress.pdf); 21 CFR 201.1, 203.3, 208.3, 314.3; Healthcare Distribution Management Association (HDMA), “HDMA Fact Sheet on PDMA,” Copyright 2010, [http://www.healthcaredistribution.org/press\\_room/pdma\\_facts.asp](http://www.healthcaredistribution.org/press_room/pdma_facts.asp); National Coalition of Pharmaceutical Distributors (NCPD), “Position paper of the National Coalition of Pharmaceutical Distributors (NCPD),” [http://www.ncpdusa.org/pdf/NCPD\\_Position\\_Paper\\_Final\\_020107.pdf](http://www.ncpdusa.org/pdf/NCPD_Position_Paper_Final_020107.pdf); and Modern Distribution Management (MDM), “2010 MDM Market Leaders: Top 10 Pharmaceutical Wholesalers,” May 27, 2010, <http://www.mdm.com/2010-mdm-market-leaders-top-10-pharmaceutical-wholesalers/PARAMS/article/26126>.

### Participants in Drug Supply Chain

A *manufacturer* produces the drug product and is usually the entity that submits the application to FDA for approval to market the product or that holds the approval.

A *wholesale distributor* sells the drug to “persons other than a consumer or patient” (21 CFR 203.3).

A *primary wholesale distributor* gets the drug products directly from the manufacturer and sells them to other wholesalers or dispensers. Three large primary wholesale distributors accounted for 85% of U.S. pharmaceutical wholesaling revenue; these are McKesson Corp., Cardinal Health Inc., and AmerisourceBergen Corp.<sup>20</sup>

An *authorized distributor of record (ADR)* is a wholesale distributor that has a relationship with a manufacturer that is ongoing, defined in regulations as including a written agreement specifying which products it will distribute and for which time period (21 CFR 203.3). Not all primary wholesalers are ADRs.

The term *secondary wholesale distributor* generally applies to wholesale distributors that acquire drug products from a wholesale distributor, not directly from the manufacturer. Some wholesale distributors focus on a region of the United States; others focus on a specialty market, say, of cancer drugs, or on the discounted drug market.<sup>21</sup>

A *repackager* removes a drug from its container and places in in another, usually smaller, container for sale to a distributor or dispenser.<sup>22</sup>

A *third-party logistics provider* may take temporary physical possession of the drug, such as during transport or warehousing, under contract with a manufacturer, distributor, or dispenser, but does not assume ownership of the drug.

A *dispenser* provides the drug to the consumer/patient. A dispenser may be an independent, community pharmacy; a retail chain pharmacy; a hospital or health care facility; a doctor’s office; etc.

In addition to the members of the supply chain, others have an interest in its functioning. The primary *federal regulator* of drug safety, and therefore the drug supply chain, is the Food and Drug Administration (FDA), joined by others, such as the Centers for Disease Control and Prevention (CDC) and the Federal Trade Commission (FTC), as warranted. A *state regulator* can be a board of pharmacy, often placed within a state department of health. *Professional and industry organizations* with interest in pharmaceutical supply chain security include those representing pharmacists, pharmacies, health care institutions, manufacturers, distributors and wholesalers, and data- and code-based technology (hardware and software) developers and maintainers.<sup>23</sup>

**Figure 1** presents the steps a finished drug product may take on its way from the manufacturer (labeled A) to the dispenser (labeled D) who will give the drug to the individual patient. This segment of the supply path is called *downstream*. The *upstream* segment ends with the

<sup>20</sup> See Pew Health Group, “After Heparin: Protecting Consumers from the Risks of Substandard and Counterfeit Drugs,” July 12, 2011, [http://prescriptionproject.org/after\\_heparin\\_report/](http://prescriptionproject.org/after_heparin_report/); and Adam Fein, “Trends and top distributors in the pharmaceuticals sector,” in MDM Market Leaders 2012: Top Pharmaceuticals Distributors, 2013, <http://www.mdm.com/2012-mdm-market-leaders-top-pharmaceuticals-distributors>.

<sup>21</sup> There were about 2,000 secondary distributors in 2007 (Pew Health Group, “After Heparin: Protecting Consumers from the Risks of Substandard and Counterfeit Drugs,” July 12, 2011, [http://prescriptionproject.org/after\\_heparin\\_report/](http://prescriptionproject.org/after_heparin_report/); and FDA, “The Prescription Drug Marketing Act: Report to Congress,” June 2001, <http://www.fda.gov/downloads/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendmentstotheFDCA/PrescriptionDrugMarketingActof1987/UCM203186.pdf>.

<sup>22</sup> U.S. Pharmacopeia, <1146> Packaging Practice—Repackaging a Single Solid Oral Drug Product into a Unit-Dose Container,” [http://www.pharmacopeia.cn/v29240/usp29nf24s0\\_c1146.html](http://www.pharmacopeia.cn/v29240/usp29nf24s0_c1146.html); and Florida Department of Business and Professional Regulation, “Prescription Drug Repackager,” <http://www.myfloridalicense.com/dbpr/ddc/PrescriptionDrugRepackager.html>.

<sup>23</sup> Examples include the American Pharmacists Association (APhA), American Society of Health-System Pharmacists (ASHP), Biotechnology Industry Organization (BIO), Generic Pharmaceutical Association (GPhA), Health Industry Distributors Association (HIDA), Healthcare Compliance Packaging Council (HCPC), Healthcare Distribution Management Association (HDMA), National Association of Boards of Pharmacy (NABP), National Association of Chain Drug Stores (NACDS), National Community Pharmacists Association (NCPA), Pharmaceutical Distribution Security Alliance (PDSA), and Pharmaceutical Research and Manufacturers of America (PhRMA).



manufacturer and involves the sources of materials that the manufacturer uses to produce the finished drug product, such as active pharmaceutical ingredients and inactive ingredients (e.g., fillers, binders, and colors).

A manufacturer may sell directly to a dispenser, but usually sells to a primary wholesale distributor (labeled B). The primary wholesale distributor may sell directly to a dispenser or may sell to a secondary wholesale distributor (labeled C) who sells it to the dispenser. A dispenser may return unopened and unexpired medication to the wholesaler who may then sell it to another dispenser or to another wholesaler or return it to the manufacturer. The combinations are numerous. Interspersed throughout the chain may be third-party logistics providers who transport or warehouse the drug under contract to the manufacturer, distributor, or dispenser.

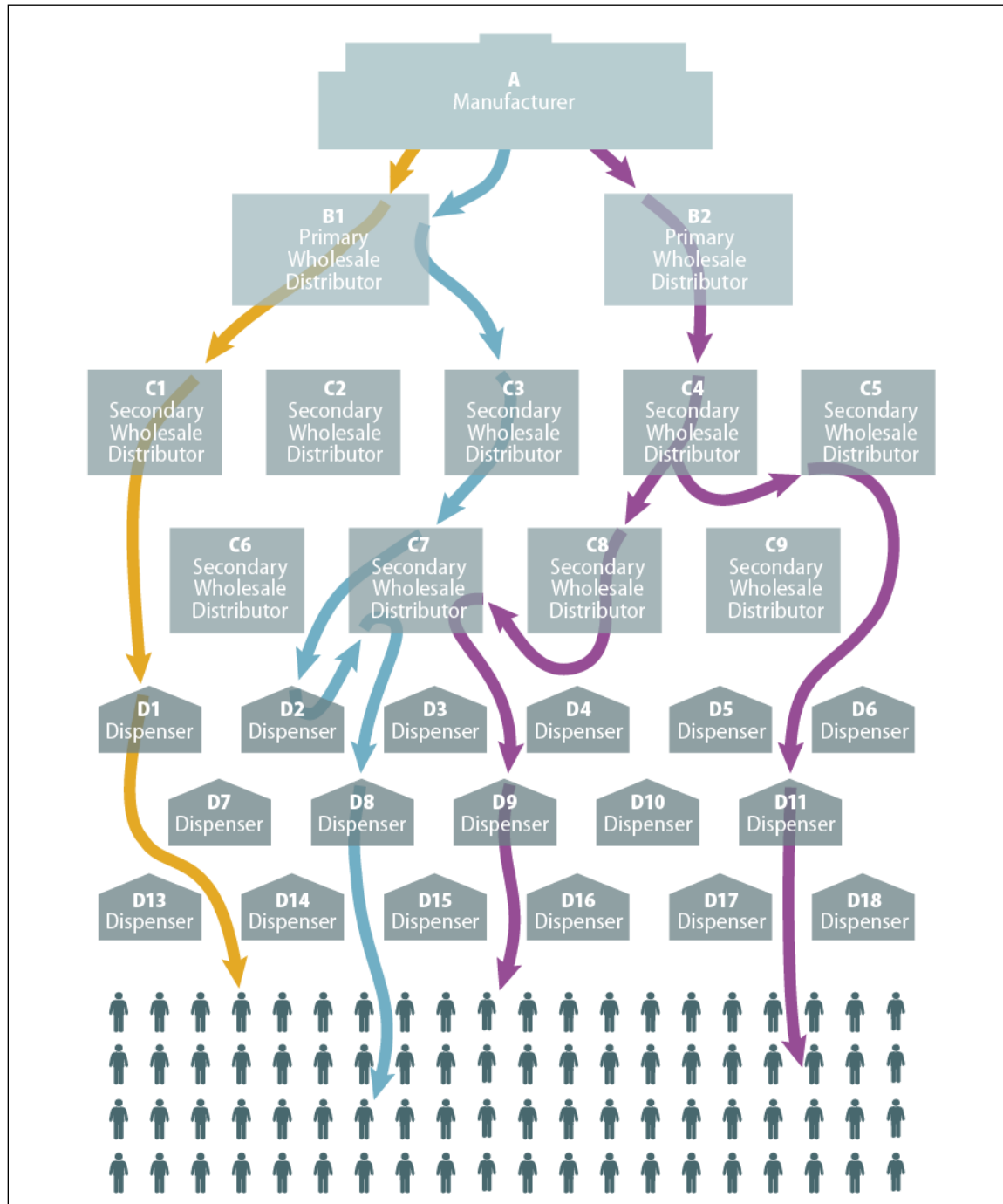
At each change of hands, the drug could be vulnerable to theft, mishandling, adulteration, and tampering;<sup>24</sup> for example, part of a legitimate shipment may be stolen for resale elsewhere and substituted with a fake. Problems may arise at other times; for example, an otherwise legitimate shipment may be inadequately refrigerated in a truck or warehouse. The colored lines in **Figure 1** illustrate alternate paths from manufacturer to patient.

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<sup>24</sup> Statement of Deborah M. Autor, Deputy Commissioner for Global Regulatory Operations and Policy, Food and Drug Administration, Department of Health and Human Services, before the Committee on Health, Education, Labor, and Pensions, United States Senate, September 14, 2011, <http://www.fda.gov/NewsEvents/Testimony/ucm271073.htm>.



**Figure I. Downstream Pharmaceutical Supply Chain**  
(for illustration)



**Source:** Prepared by CRS.

## How Congress Has Moved to Regulate the Supply Chain

FDA's earliest authorities, in 1906, concerned product integrity. Subsequent changes in the law related to product integrity and safety reflected the mid-century pharmaceutical industry with mostly domestic factories. Since its passage in 1938, the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended, both directly addresses and indirectly influences the pharmaceutical supply chain. Relevant FFDCA sections cover topics including prohibitions and penalties regarding adulterated or misbranded drugs (e.g., Sections 301, 303, 501, and 502), pharmaceutical security (e.g., Section 505D), registration and inspection of producers and facilities (e.g., Sections 510 and 704), and imports and exports (e.g., Section 801), among others.

In the last quarter century, Congress has made three focused attempts at improving supply chain security by amending the FFDCA. Each one added tools—standards, penalties, required planning—to strengthen federal oversight of the supply chain, as described below. Gaps, however, remain.

### Prescription Drug Marketing Act of 1987

In the 1980s, Congress determined that the drug distribution system was not sufficiently “closed” to prevent abuse of drug samples. The Prescription Drug Marketing Act of 1987 (PDMA, P.L. 100-293)<sup>25</sup> amended FFDCA Section 503. It banned the sale, trade, and purchase of drug samples, and mandated storage, handling, and accounting standards for drug samples. By adding a new Subsection 503(e), PDMA also addressed other segments of the supply chain with the following changes to the FFDCA:

- required that wholesalers, except for authorized distributors of record, provide to the recipient “a statement ... identifying each prior sale, purchase, or trade of such drug....,” often referred to as a pedigree;
- required each manufacturer to maintain a current list of its authorized distributors of record;
- stated that no one may engage in wholesale distribution unless licensed by a state in accordance with the Secretary’s guidelines;
- required the Secretary<sup>26</sup> to issue guidelines, by regulation, establishing minimum standards for wholesaler licensing to include storage and handling and records;
- and defined *authorized distributor of record (ADR)* and *wholesale distribution* (see earlier textbox).

PDMA also established civil and criminal penalties for violations of its provisions.

Implementation of FFDCA Section 503(e)—in particular the first bullet, above—has not gone smoothly. To enforce the law, the FDA drafted regulations that would require drug companies to maintain a detailed “chain of custody” (also known as a pedigree) for every pharmaceutical

<sup>25</sup> U.S. Congress, House Committee on Energy and Commerce, *Prescription Drug Marketing Act of 1987*, H.Rept. 100-76, 100<sup>th</sup> Cong., 1<sup>st</sup> Sess. Washington, GPO, April 30, 1987, p. 7. Congress amended and clarified some PDMA provisions in the Prescription Drug Amendments (PDA) of 1992, P.L. 102-353.

<sup>26</sup> In this report, the Secretary means the Secretary of Health and Human Services.

product sold in this country.<sup>27</sup> The recorded pedigree would allow manufacturers to trace back suspected counterfeit shipments. FFDCA Section 503(e)(1)(A) [21 U.S.C. 353(e)(1)(A)] states:<sup>28</sup>

Each person who is engaged in the wholesale distribution of a drug subject to subsection (b) of this section [a prescription drug] and who is not the manufacturer or an authorized distributor of record of such drug shall, before each wholesale distribution of such drug (including each distribution to an authorized distributor of record or to a retail pharmacy), provide to the person who receives the drug a statement (in such form and containing such information as the Secretary may require) identifying each prior sale, purchase, or trade of such drug (including the date of the transaction and the names and addresses of all parties to the transaction).

However, the law specifically excluded manufacturers' authorized distributors of record (ADRs) from this pedigree requirement. Because ADRs sell most drugs into secondary drug wholesale distribution markets, the PDMA recordkeeping requirement created a dilemma. Because the law does not require that a manufacturer or an ADR give the records or pedigree with the drugs, the secondary distributors do not necessarily have the chain-of-custody information that the law requires them to provide to their customers.

For that reason, when FDA published final regulations to implement this section of the PDMA in December 1999,<sup>29</sup> the Small Business Administration petitioned the agency, arguing that enforcement of the provision would drive 4,000 or more secondary distributors out of business. Subsequently, FDA delayed the effective date of this provision's enforcement repeatedly,<sup>30</sup> most recently because it believed that industry voluntary conversion to an electronic pedigree was imminent, in which case the rule would be superfluous. In November 2006, FDA announced the availability of a compliance policy guide (CPG 160.900) regarding the December 1, 2006, implementation of its PDMA pedigree regulations (21 CFR 203.3(u) and 203.50)), along with a guidance for industry to answer questions about PDMA requirements.<sup>31</sup> One week later, a court issued a preliminary injunction to prohibit FDA's implementing key pieces of the rule and FDA

<sup>27</sup> By imposing strict recordkeeping requirements, FDA hoped, among other things, to ensure the safety and quality of all drugs that are exported and later imported back into the country (FDA, "The Prescription Drug Marketing Act: Report to Congress," 2001, [http://www.globalcompliance.com/pdf/Prescription%20Drug%20Marketing%20Act%20\(PDMA\)%20Report%20to%20Congress.pdf](http://www.globalcompliance.com/pdf/Prescription%20Drug%20Marketing%20Act%20(PDMA)%20Report%20to%20Congress.pdf)); and 21 CFR part 203 (Prescription Drug Marketing).

<sup>28</sup> FFDCA Section 503(e); and H.Rept. 100-76 [to accompany H.R. 1207], Mr. Dingell, April 30, 1987.

<sup>29</sup> FDA had previously issued a guidance letter in August 1988 (Attachment E to FDA, "Prescription Drug Marketing Act Report to Congress," June 2001, <http://www.fda.gov/downloads/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticAct/FDCA/SignificantAmendments/totheFDCA/PrescriptionDrugMarketingActof1987/UCM203186.pdf>, see PDF pages 50-65) and a proposed rule in March 1994 (FDA, "21 CFR Parts 203 and 205 [Docket No. 92N-0297] RIN 0905-AC81, Prescription Drug Marketing Act of 1987; Prescription Drug Amendments of 1992; Policies, Requirements, and Administrative Procedures; Proposed rule," *Federal Register*, vol. 59, No. 49, March 14, 1994, <http://www.gpo.gov/fdsys/pkg/FR-1994-03-14/html/94-5540.htm>).

<sup>30</sup> FDA, "Prescription Drug Marketing Act of 1987; Prescription Drug Amendments of 1992; Policies, Requirements, and Administrative Procedures; Delay of Effective Date," *Federal Register*, February 23, 2004 (21 CFR 203). For PDMA history, see <http://www.fda.gov/oc/pdma/report2001/report.html>, p. 7.

<sup>31</sup> FDA, "Prescription Drug Marketing Act Pedigree Requirements under 21 CFR Part 203 Compliance Guide and Guidance for Industry: Prescription Drug Marketing Act Pedigree Requirements Questions and Answers; Notice of availability of guidances," *Federal Register*, vol. 71, no. 220, November 15, 2006, pp. 66448-66450, <http://www.gpo.gov/fdsys/pkg/FR-2006-11-15/pdf/06-9211.pdf>; FDA, "Compliance Policy Guide (CPG) 160.900 Prescription Drug Marketing Act—Pedigree Requirements under 21 CFR Part 203," November 2006, <http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm073857.htm>; and FDA, "Prescription Drug Marketing Act (PDMA) Requirements: Questions and Answers," Center for Drug Evaluation and Research, Office of the Commissioner, Office of Regulatory Affairs, November 2006, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM134399.pdf>.

published an addendum to its guidance for industry, describing the injunction's effect on various elements of the regulatory requirements.<sup>32</sup> In March 2010, FDA stated that, "As a result of this litigation, FDA has been exercising its enforcement discretion concerning the drug pedigree requirements and only requiring that drug pedigrees go back to the last 'authorized distributor of record.'"<sup>33</sup> In July 2011, FDA issued a proposed rule to remove its rule on pedigree requirements for wholesale distribution (21 CFR 203.50(a)).<sup>34</sup>

## Food and Drug Administration Amendments Act of 2007

The PDMA chain-of-custody requirements are not the only provisions in the FFDCA that address the security of the pharmaceutical supply chain.

With the FDA Amendments Act of 2007 (FDAAA, P.L. 110-85), Congress added FFDCA Section 505D [21 U.S.C. 355d] "Pharmaceutical Security."<sup>35</sup> The law directed the Secretary to "develop standards and identify and validate effective technologies for the purpose of securing the drug supply chain against counterfeit, diverted, subpotent, substandard, adulterated, misbranded, or expired drugs." In particular, the law required the Secretary to

develop a standardized numerical identifier (which, to the extent practicable, shall be harmonized with international consensus standards for such an identifier) to be applied to a prescription drug at the point of manufacturing and repackaging (in which case the numerical identifier shall be linked to the numerical identifier applied at the point of manufacturing) at the package or pallet level, sufficient to facilitate the identification, validation, authentication, and tracking and tracing of the prescription drug.

Complying with that requirement, FDA issued "Draft Guidance for Industry on Standards for Securing the Drug Supply Chain—Standardized Numerical Identification for Prescription Drug Packages" in January 2009.<sup>36</sup> The agency issued the final guidance in March 2010.<sup>37</sup> Note that FDAAA did not authorize the Secretary to *require* the use of SNIs. Action on use of an SNI will likely depend on future legislation.

FDAAA also directed the Secretary to undertake other activities. They fall into three general areas: addressing promising technologies, such as radiofrequency identification technology, nanotechnology, encryption technologies, and other track-and-trace technologies; undertaking

<sup>32</sup> FDA, "Addendum to FDA's 'Guidance for Industry: PDMA Pedigree Requirements—Questions and Answers' Related to the Preliminary Injunction ordered 12/5/06 in *RxUSA Wholesalers, Inc. v. HHS*," December 15, 2006, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM134399.pdf>.

<sup>33</sup> FDA, "Chapter 2. FDA Authority," *Regulatory Procedures Manual*, March 2010, <http://www.fda.gov/downloads/ICECI/ComplianceManuals/RegulatoryProceduresManual/UCM074340.pdf>.

<sup>34</sup> In the *Federal Register* notice, FDA wrote, "We note that even with the removal of § 203.50(a), the pedigree requirements of section 503(e)(1)(A) of the FD&C Act would still be in effect" (FDA, "[Docket No. FDA-2011-N-0446] Removal of Certain Requirements Related to the Prescription Drug Marketing Act; Opportunity for Public Comment; Proposed rule," *Federal Register*, vol. 76, no. 135, July 14, 2011, pp. 41434-41438, <http://www.gpo.gov/fdsys/pkg/FR-2011-07-14/pdf/2011-17696.pdf>). Later, FDA noted that the case (*RxUSA Wholesale, Inc. v. HHS*) had ended and proposed withdrawing Section. 203.50(a) (*Federal Register*, vol. 77, no. 29, February 13, 2012, p. 7949).

<sup>35</sup> For the pharmaceutical security and other provisions in FDAAA, see CRS Report RL34465, *FDA Amendments Act of 2007 (P.L. 110-85)*, by Susan Thaul.

<sup>36</sup> *Federal Register*, v. 74, no. 11, January 16, 2009, pp. 3054-3055.

<sup>37</sup> FDA, "Guidance for Industry: Standards for Securing the Drug Supply Chain—Standardized Numerical Identification for Prescription Drug Packages," Office of the Commissioner, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, and Office of Regulatory Affairs, March 2010, <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM206075.pdf>.

enhanced and joint enforcement activities with other federal and state agencies; and establishing regional capabilities for validation and inspection.<sup>38</sup>

## Food and Drug Administration Safety and Innovation Act of 2012

Five years after FDAAA, attempts by Congress, FDA, and other stakeholders to craft a comprehensive supply chain plan culminated in the Food and Drug Administration Safety and Innovation Act (FDASIA, P.L. 112-144). Members, committees, bipartisan and bicameral staff groups, and stakeholder groups had released several bills and discussion drafts in the 112<sup>th</sup> Congress in advance of FDASIA.<sup>39</sup> Although all parties expressed willingness to compromise because of the urgent need to find solutions to security threats and the complications that would arise if each state went its own way with laws and regulations, they were unable to agree on a complete approach.

FDASIA, as enacted, expanded FDA authority regarding manufacturer registration, facility inspection, and importation.<sup>40</sup> It included provisions to allow FDA to refuse entry of an imported drug if the manufacturing facility inspection was denied or limited; enhance penalties for suppliers of counterfeit or substandard products; and require a unique manufacturing facility identifier for both domestic and foreign facilities. (The following textbox provides a longer summary of the FDAAA drug supply chain provisions.)

<sup>38</sup> For more information on supply chain technologies, see, for example, Lisa A Daigle, "Following Pharmaceutical Products Through the Supply Chain," ASHP (American Society of Health-System Pharmacists) Policy Analysis, August 2012, <http://www.ashp.org/DocLibrary/Advocacy/AnalysisPaper/Following-Pharmaceutical-Products.aspx>; and materials from a February 2011 FDA public workshop, "Determination of System Attributes for the Tracking and Tracing of Prescription Drugs," <http://www.fda.gov/downloads/Drugs/NewsEvents/UCM245540.pdf>.

<sup>39</sup> Legislative attempts in the 112<sup>th</sup> Congress included, for example, H.R. 1483 (Representatives Dingell, Waxman, Pallone, and DeGette); H.R. 3026 (Representatives Matheson and Bilbray); a March 16, 2012 discussion draft (Senators Bennet and Burr); RxTEC (a February 2012 draft from the Pharmaceutical Distribution Security Alliance (PDSA)); S. 3187 (§722 as passed by Senate); and several proposals discussed during FDASIA negotiations.

<sup>40</sup> For more detail on the supply chain and other provisions of FDASIA, see CRS Report R42680, *The Food and Drug Administration Safety and Innovation Act (FDASIA, P.L. 112-144)*, coordinated by Susan Thaul. To compare the House- and Senate-passed versions of the bills, see CRS Report R42564, *FDA User Fees and the Regulation of Drugs, Biologics, and Devices: Comparative Analysis of S. 3187 and H.R. 5651*, coordinated by Susan Thaul.

### **FDASIA Drug Supply Chain Provisions<sup>41</sup>**

In general, Title VII, Drug Supply Chain:

- Expanded the registration information required from the owners or operators of domestic and foreign drug establishments to include a unique facility identifier and information about importers.
- Expanded registration information required to include establishments that manufacture excipients (such as fillers, preservatives, and flavors) for listed products.
- Required the Secretary to maintain an electronic database of unique facility identifiers.
- Required the Secretary to carry out manufacturing establishment inspections according to a risk-based schedule for both prescription and nonprescription drugs; specified risk factors and required reports.
- Required manufacturers to submit required records in advance or in lieu of inspections within a reasonable timeframe; and required the Secretary to sufficiently describe the records requested and to provide receipt confirmations.
- Required that a drug be deemed adulterated if the owner or operator of a facility used in its manufacture delays, denies, or limits an inspection, or refuses to permit entry or inspection.
- Allowed the Secretary to destroy an adulterated, misbranded, or counterfeit drug offered for import if it is valued at \$2,500 or less; and included language about notice, storage, cost liability, and regulations.
- Expanded the Secretary's authority to administratively detain a product found to be adulterated or misbranded during a facility inspection to include drugs (prior authority was for device and tobacco products).
- Allowed the Secretary to, in specified conditions, keep confidential the information relating to drug inspections that a foreign government provided voluntarily.
- Noted that, with respect to the criteria for deeming a drug to be adulterated, "current good manufacturing practices" include quality controls in manufacturing, and assurance of the safety of raw materials.
- Allowed the Secretary to enter into agreements with foreign governments to recognize inspections of foreign establishments in specified situations.
- Allowed the Secretary to require, as a condition of granting a drug admission to the United States, an importer to provide specified information demonstrating that the drug complies with requirements of this act.
- Required a commercial importer to register with the Secretary and submit, among other things, a unique facility identifier; required the Secretary to promulgate regulations to establish good importer practices; and prohibited the importation of drugs by unregistered commercial importers.
- Allowed the Secretary to require that a registered manufacturer, a wholesaler, or a distributor (other than for retail sale) notify the Secretary when that person knows (1) that the use of a drug may result in serious illness or death; (2) of a significant theft of such drug; or (3) of the counterfeiting of such drug that is in U.S. commerce or could be imported.
- Required imprisonment for up to 20 years or a fine up to \$1 million for a person who knowingly and intentionally adulterates a drug so that the drug has a reasonable probability of causing serious adverse health consequences or death to humans or animals.
- Added trafficking in a counterfeit drug to the list of violations subject to fines and imprisonment under the U.S. criminal and penal code, and directed the U.S. Sentencing Commission to amend guidelines to increase penalties to reflect the serious nature of these offenses.
- Asserted U.S. authority to enforce the FFDCA for a violation that occurs outside the United States if the product was intended for U.S. import or if an act committed in the United States furthers the violation.

Although FDASIA included several elements of a broader plan, key items, such as chain-of-custody documentation and track-and-trace technologies, remained unresolved. Following

<sup>41</sup> The drug supply chain provisions in Title VII of FDASIA amended FFDCA Sections 301, 303, 304, 501, 502, 510, 704, 708, 801; added new FFDCA Sections 568 and 809; and amended 18 U.S.C. 2320.



FDASIA passage, Members and staff continued discussions, attempting to find an effective and feasible mix would cover domestic and foreign facilities.<sup>42</sup>

## State Activity

In the absence of a federal plan, about half of all states have passed their own laws to address drug pedigrees and supply chain security.<sup>43</sup> Legislation is pending in some other states. The approaches and extent of law and regulation vary by state, but they generally address similar issues such as definitions, licensing, permits, registration, pedigrees, and recordkeeping, among other topics.

In discussing federal proposals for a uniform national system, Members of Congress as well as stakeholders testifying at congressional hearings often refer to the law that California first passed in 2004 and then amended (regarding implementation dates) in 2006 and 2008.<sup>44</sup> The California law now calls for its pedigree requirements to go into effect in 2015.

Central to the California law is a required electronic pedigree to include every transaction from the manufacturer to the dispenser of the prescription drug.<sup>45</sup> The pedigree is to include information about the seller (e.g., identifying information and registration number), the drug (e.g., name, quantity, dose, expiration date, lot numbers, and a unique identification number), and the shipment (e.g., size and number of containers, and invoice number). The pedigree data must be handled in a system that is interoperable, “ensuring compatibility throughout all states of distribution.” The law provides definitions and exemptions (e.g., medical gases and drugs for veterinary use).

One provision of the California law<sup>46</sup> is particularly relevant for federal policymakers:

Upon the effective date of federal legislation or adoption of a federal regulation addressing pedigree or serialization measures for dangerous drugs, Sections ... shall become inoperative.

Members of Congress who want a comprehensive supply chain law (such as what California has enacted) may not want to pass a less extensive federal law because it could prevent California

<sup>42</sup> “As Congress Continues to Mull Track and Trace, California Plows Ahead on ePedigree,” *Drug Industry Daily*, August 3, 2012.

<sup>43</sup> Two 2011 reports by the National Alliance for Model State Drug Laws (NAMSDL) described pedigree-related statutes in 20 states and regulations in 16 states (NAMSDL, “Drug Pedigree Requirements for Pharmacies and Wholesalers: State Statutes,” July 2011, <http://www.namsdl.org/documents/StateStatutoryCompilationJuly2011.pdf>; and NAMSDL, “Drug Pedigree Requirements for Pharmacies and Wholesalers: State Regulations,” July 2011, <http://www.namsdl.org/documents/StateRegulatoryCompilationJuly2011.pdf>). According to 2013 testimony from the Healthcare Distribution Management Association (HDMA), 29 states have laws or regulations that go “beyond the federal PDMA standards” (Testimony of Elizabeth A. Gallenagh, Vice President, Government Affairs and General Counsel, Healthcare Distribution Management Association, before the House Energy and Commerce Committee, Subcommittee on Health, April 25, 2013, [http://www.healthcaredistribution.org/testimony/2013-04-25\\_gallenagh\\_testimony.pdf](http://www.healthcaredistribution.org/testimony/2013-04-25_gallenagh_testimony.pdf)).

<sup>44</sup> California Department of Consumer Affairs, Board of Pharmacy, “California E-Pedigree Law,” [http://www.pharmacy.ca.gov/about/e\\_pedigree\\_laws.shtml](http://www.pharmacy.ca.gov/about/e_pedigree_laws.shtml). This webpage has links to “Background and Summary of E-Pedigree Laws,” California Business and Professions Code sections, PowerPoint “Overview of the Law, questions and answers document, and text of the law.

<sup>45</sup> The actual language in the California pedigree provision refers to a “dangerous drug.” However, elsewhere in the California code that term is defined to mean a prescription drug.

<sup>46</sup> California Board of Pharmacy, “Section 4034.1. Enactment of Federal Pedigree Legislation,” 2013 Lawbook for Pharmacy, [http://www.pharmacy.ca.gov/laws\\_regs/lawbook.pdf](http://www.pharmacy.ca.gov/laws_regs/lawbook.pdf).



from implementing its pedigree requirements. Some manufacturers and distributors have cautioned that not only are the California requirements expensive but they rely on technologies that are not fully formed. Others report that the technologies are sufficiently advanced and they have already begun gearing up to comply with the California law.

## Professional and Industry Association Activity

Several associations and ad hoc alliances of industry participants recommended supply chain security systems or proposed legislation that they could support.

The **National Association of Boards of Pharmacy (NABP)** has worked with states to create a Model State Pharmacy Act and Model Rules.<sup>47</sup> The 2010 Model Act defines *wholesale distributor*<sup>48</sup> and recommends the adoption of *electronic pedigrees* subject to the availability of adequate technology.

NABP has also developed criteria and a process to accredit distributors. NABP's website describes its Verified-Accredited Wholesale Distributors (VAWD) program, established in 2004 and updated in May 2013, and notes that 21 states recognize VAWD, including 3 that require it.<sup>49</sup> NABP describes the VAWD program as follows:

Wholesale distributors that display the VAWD Seal as part of their accreditation have undergone a criteria compliance review, including a rigorous review of their operating policies and procedures, licensure verification, survey of facility and operations, background checks, and screening through the NABP Clearinghouse. Accredited facilities are reviewed annually and undergo a site survey every three years.

The **Pharmaceutical Distribution Security Alliance (PDSA)** issued draft legislative language in February 2012: the Pharmaceutical Traceability Enhancement Code (RxTEC) Act.<sup>50</sup> The draft would create a comprehensive system involving a machine-readable graphic on individual packages to support lot-level tracing of a product to its immediate previous and subsequent owners. The system would be implemented incrementally, with manufacturer, repackager, wholesale distributor, and dispenser requirements beginning three, four, five, and six years, respectively, after enactment.

<sup>47</sup> National Association of Boards of Pharmacy (NABP), "Model State Pharmacy Act and Model Rules of the National Association of Boards of Pharmacy," August 2010, <http://www.nabp.net/publications/model-act>.

<sup>48</sup> NABP's Model Act defines wholesale distributor as "including but not limited to Manufacturers, Repackagers, own-label distributors, private-label distributors, jobbers, brokers, warehouses, including Manufacturers' and Distributors' warehouses, Co-licensees, Exclusive Distributors, Third-Party Logistics Providers, Chain Pharmacy Warehouses, and Wholesale Drug warehouses, independent Wholesale Drug traders, and retail Pharmacies that conduct Wholesale Distributions" (National Association of Boards of Pharmacy (NABP), "Model State Pharmacy Act and Model Rules of the National Association of Boards of Pharmacy," August 2010, <http://www.nabp.net/publications/model-act>).

<sup>49</sup> NABP, "VAWD [Verified-Accredited Wholesale Distributors]," 2013, <http://www.nabp.net/programs/accreditation/vawd>; and NABP, "NABP Updates VAWD Criteria, Continuing Efforts to Help Secure the Integrity of US Drug Supply Chain for the Protection of Public Health," May 8, 2013, <http://www.nabp.net/news/nabp-updates-vawd-criteria-continuing-efforts-to-help-secure-the-integrity-of-us-drug-supply-chain-for-the-protection-of-public-health—2>.

<sup>50</sup> Pharmaceutical Distribution Security Alliance (PDSA), "Pharmaceutical Traceability Enhancement Code (RxTEC) Act," February 27, 2012 Discussion Draft; link to summary is available on the Health Industry Distributors Association (HIDA) website at <http://www.hida.org>.

## Policy Decision Points

Versions of pharmaceutical supply chain legislation have been considered in both the House and Senate in the 113<sup>th</sup> Congress.<sup>51</sup> This report is designed as a backgrounder for those new to the issue, thus it does not track current legislation.

All parties to the discussion agree to one big-picture goal: pharmaceutical supply chain security. Several sub-goals, some of them overlapping, are evident in current and prior legislative proposals that would

- *protect the patient* from ineffective or dangerous drugs that may be in the supply chain as a result of counterfeiting, theft and resale, or manufacturing, transportation, or storage mishaps;
- *protect the manufacturer*, who can lose both money and reputation if its product harms a patient, regardless of whether the fault laid with the manufacturer's actions; and
- *allow* the assignment of accountability for identified problems.

In working toward those subgoals, policymakers are also trying to

- *avoid* having to comply with *diverse state requirements* by enacting a national plan; and
- establish a system that is logistically *feasible at manageable cost*.

Although Congress, FDA, and affected industry and health care stakeholders agree on an overall goal (increasing supply chain security), they have disagreed about approaches and details. The drafters and negotiators of legislative language face many policy decision points. Some policy decision points involve *whether to do* something at all (e.g., Is the current system of state regulation better than proposed federal changes?). Others would involve the implementation *timing* of a requirement (e.g., implement six months or 10 years after enactment, study and consider recommendations six months or 10 years after enactment, or implement in clearly defined action and timing stages); or the *scope* of a requirement (e.g., types of drugs, types of facilities, time period covered, timing of activity).

The following section lays out many of the terms and policy decision points under discussion by Members, committees, and staff of Congress. Each paragraph presents a term (e.g., track and trace) under discussion and a very brief suggestion of how it fits into the overall attempt to regulate the pharmaceutical supply chain.

*Definitions.* Different industries, professions, and statutes use similar terms differently.<sup>52</sup> In creating legislation for pharmaceutical supply chain security, policymakers must decide how to

<sup>51</sup> After posting two discussion drafts, the House Committee on Energy and Commerce reported a bill that the House passed on June 3, 2013: H.R. 1919, the Safeguarding America's Pharmaceuticals Act of 2013. The Senate Committee on Health, Education, Labor, and Pensions, after posting a discussion draft, voted to favorably report S. 957, the Drug Supply Chain Security Act.

<sup>52</sup> A February 2013 report from the Institute of Medicine (IOM) begins with a discussion of "the competing and often overlapping definitions of the terms *counterfeit*, *falsified*, and *substandard*" and how different usage in legal and public health contexts can muddy policy discussions (IOM, *Countering the Problem of Falsified and Substandard Drugs*, Gillian J. Buckley and Lawrence O. Gostin, editors, Washington DC: National Academies Press, 2013).

define the meaning of terms they use. For example, wholesaler, distributor, third-party logistics provider, manufacturer, pharmacy, package, and pedigree.<sup>53</sup>

*Pedigree.* A description of the drug (possibly information such as name, amount, dosage, manufacturer, lot number) and a statement of the transaction history of the drug, including each transfer of ownership (and/or physical possession) of the product. This could include seller, purchaser, amount transferred, lot numbers, among other information. Current movement is away from paper toward an electronic pedigree.

*Track and trace.* A system that involves electronically tagging each package with a unique identifier (serialization), noting each transfer of a drug package, and maintaining a database of all such transactions.<sup>54</sup> For example, a manufacturer might want to track a package to facilitate a recall if a problem were noted. A public health authority (or the manufacturer) might want to trace back to where a package has been to determine the source of a local problem.

*Serialization (SNI—standardized numerical identifier).* A mark placed on a package at the manufacturing facility (and again at the time of repackaging) that is unique to that package. As FDAAA required, the Secretary has developed a standardized numerical identifier (SNI). FFDCA, including FDAAA amendments, does not give the Secretary authority to require the use of SNIs.

*Lot- or unit-level activity.* Whether a labeling or tracking requirement applies at the level of the lot or the unit. A lot is the full output of a manufacturer's production run; it can include thousands of units. A unit is the smallest package that is delivered to the dispenser (retail or hospital pharmacy or clinical setting) who will dispense it to a patient. The use of unit-level tracking and tracing could allow quicker and more focused recalls and real-time investigation of adverse events. This more extensive approach would also be more expensive. Some proposals would separate the labeling task from the reporting task in setting implementation goals or requirements.

*Supply chain.* Analysts speak of the *upstream* supply chain (sources and path of ingredients that go to the manufacturer) and the *downstream* supply chain (path of the finished product after it leaves the manufacturer). Current legislative discussions are focused on the downstream chain. For each requirement regarding pedigrees/transaction records, authentication/verification, and other supply chain security activities, legislation could specify start and end points; however, opinions differ on which points to use.<sup>55</sup> The most inclusive (and with higher up-front costs for supply-chain participants) would cover all transactions beginning with the manufacturer and ending with retail sale to the patient.

<sup>53</sup> In layman vocabulary, for example, the term *package* could apply to any of the following deliveries: the package the patient picks up at the drug store with, for example, 30 tablets; or the package of 100 bottles each with 250 tablets that the secondary distributor delivers to the drug store; or the package with 1000 of the 250-tablet bottles or 500 cartons each with four 2000-tablet jugs. If the legislative language does not clearly define what package means when it requires something at the package level (e.g., a standardized numerical identifier, tracking and tracing to the package level within a certain amount of time), that ambiguity may cause problems in implementation.

<sup>54</sup> See, for example, Pew Health Group, "After Heparin: Protecting Consumers from the Risks of Substandard and Counterfeit Drugs," July 12, 2011, [http://prescriptionproject.org/after\\_heparin\\_report/](http://prescriptionproject.org/after_heparin_report/); and FDA, "The Prescription Drug Marketing Act: Report to Congress," June 2001, <http://www.fda.gov/downloads/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendmentsTotheFDCA/PrescriptionDrugMarketingActof1987/UCM203186.pdf>.

<sup>55</sup> Questions include whether to require a retail pharmacy or a hospital pharmacy to track what it dispenses in addition to what it receives. Obstacles include the need for scanners and staff time (see, for example, Lisa Daigle, "Following Pharmaceutical Products Through the Supply Chain," American Society of Health-System Pharmacists (ASHP) Policy Analysis, August 2012, <http://www.ashp.org/DocLibrary/Advocacy/AnalysisPaper/Following-Pharmaceutical-Products.aspx>).

*Authentication.* When accepting a shipment, the recipient (e.g., distributor, warehouse, or dispenser) could be required to verify the SNI and the distribution history.

*Technology choice.* Under a track-and-trace system, an SNI would be applied at the manufacturer or repackager level to each package. Information about contents and its distribution path could be included or linked. Analysts debate the benefits and limitations of various technologies such as two-dimensional bar codes or radio-frequency identification (RFID) for track and trace purposes. Further, the technologies are evolving as packaging and data management engineers are designing other systems for supply chain use.

*Interoperability.* For a track and trace system to work as envisioned, the data maintained by the manufacturer and each subsequent link in the chain must have compatible formats and definitions. Interoperability would also apply to the way data are communicated (e.g., a standardized language) and interpreted by those contributing to or using the data.

*Data management.* In a track-and-trace system, some entity would maintain standards on how participants collect, store, protect, and use data. Such management could be centralized or decentralized (distributed), each approach having benefits and limitations.<sup>56</sup>

*Data access.* Policymakers could specify in legislation several choices regarding data access—such as who would have access to which data elements—or leave it to the responsible agency (most likely FDA) to establish by regulation and guidance. Considerations might include for what purposes someone might use the data; and whether the user would need real-time data to track an unknown contaminant or could use semi-annual records for reports.

*Confidentiality.* Decisions about data management and access could involve consideration of the confidentiality of information about patients, dispensers, clinicians, and business entities across the supply chain.

*Notification.* Distributors or dispensers may find that a shipment includes suspected or confirmed counterfeit or substandard drug products. A new law might require that they notify other supply chain participants. The law or subsequent regulations could direct how the data management group or the overseeing federal agency could manage that information.

*Penalties.* Legislation could specify whether penalties (civil and/or criminal) would apply to various violations of compliance with provisions relating to, for example, labeling or completing transaction records. FFDCA already allows penalties for, among other violations, acts of counterfeiting, misbranding, and marketing of unapproved drugs.

*Implementation timing.* Various legislative proposals set different time frames for each step—for example, use of SNI, lot-level transaction reporting, unit-level transaction reporting, and issuance of proposed and final regulations.

*Licensure, registration, and accreditation.* In general, states choose whether and how to license members of professions and specific activities. At the federal level, FDA requires entities to register with FDA if they participate in specified activities; for example, a manufacturer of a drug

<sup>56</sup> FDA held a public workshop, “Determination of System Attributes for the Tracking and Tracing of Prescription Drugs,” in February 2011. Links to the agenda, discussion topics, PowerPoint slides, and workshop summary are at <http://www.fda.gov/Drugs/NewsEvents/ucm239382.htm>. Introductory material referred to the need for “standardized practices in data format, data communications, and data interpretation” (FDA, “FDA Track and Trace Public Workshop,” February 15-16, 2011, slide 23, <http://www.fda.gov/downloads/Drugs/NewsEvents/UCM245540.pdf>).

in commercial distribution.<sup>57</sup> Some legislative proposals address the federal role in licensing standards for wholesale distributors and other members of the supply chain.

*Accountability.* Registration of supply chain participants would support assigning or accepting accountability for errors, accidents, and weaknesses along the chain. How a supply chain security system is structured could affect how foreign participants engage with the recordkeeping and how FDA could manage oversight and enforcement of compliance.<sup>58</sup>

*Cost.* Consideration of cost is often a part of decisions regarding scope, implementation dates, reporting requirements, and other elements of a supply chain security system. Issues raised include who bears the cost (e.g., manufacturer, patient, government, distributors, dispensers); what the cost would be given current technology and systems; and what it might be if new products are developed in response to new requirements.

*Federal and state jurisdiction.* There seems to be general agreement that a uniform set of national standards has advantages over a patchwork of varying state requirements. However, the requirements in federal legislation might *preempt* state law and regulation. Those who favor the more extensive requirements that some states (such as California) have enacted would prefer that federal requirements be a floor upon which states could choose to build.

## Concluding Comments

As drug production has shifted to a global supply chain of manufacturers, processors, packagers, importers, and distributors,<sup>59</sup> FDA leadership, among others, has suggested that the agency's current statutory authority does not match its responsibilities to ensure that the nation's drug supply is secure.<sup>60</sup> In April 2013, FDA's Dr. Woodcock testified,<sup>61</sup>

A robust track-and-trace system, in which each drug produced would be tracked as it passes through the distribution system and allows purchasers to verify its distribution history, would improve the ability to identify and detect potentially harmful products if they enter the supply chain. Another potential benefit would be to improve the efficiency of product recalls. Imagine a system that enables the distributor or pharmacist to readily determine if they have sold or now have in stock a drug that had been identified as a counterfeit or subject to a recall. They could quickly remove that product from the supply chain, keeping the patient out of harm's way. The only way this can be done effectively is if all supply

<sup>57</sup> 21 CFR Part 207—Registration of Producers of Drugs and Listing of Drugs in Commercial Distribution.

<sup>58</sup> Pew Health Group, "After Heparin: Protecting Consumers from the Risks of Substandard and Counterfeit Drugs," July 12, 2011, [http://prescriptionproject.org/after\\_heparin\\_report/](http://prescriptionproject.org/after_heparin_report/).

<sup>59</sup> See, for example, FDA, "A Special Report: Pathway to Global Product Safety and Quality," July 2011, <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OC/GlobalProductPathway/UCM262528.pdf>; and Pew Health Group, "After Heparin: Protecting Consumers from the Risks of Substandard and Counterfeit Drugs," July 12, 2011, [http://prescriptionproject.org/after\\_heparin\\_report/](http://prescriptionproject.org/after_heparin_report/).

<sup>60</sup> Statement of Deborah M. Autor, Deputy Commissioner for Global Regulatory Operations and Policy, FDA, before the Senate Committee on Health, Education, Labor, and Pensions, "Securing the Pharmaceutical Supply Chain," September 14, 2011, <http://www.fda.gov/NewsEvents/Testimony/ucm271073.htm>; and statement of Janet Woodcock, Director, FDA Center for Drug Evaluation and Research, before the Subcommittee on Oversight and Investigations, House Committee on Energy and Commerce, "FDA's Ongoing Heparin Investigation," April 29, 2008, <http://www.fda.gov/NewsEvents/Testimony/ucm115242.htm>.

<sup>61</sup> Statement of Janet Woodcock, Director, Center for Drug Evaluation and Research, Food and Drug Administration, Department of Health and Human Services, before the Subcommittee on Health, Committee on Energy and Commerce, U.S. House of Representatives, hearing on "Securing Our Nation's Prescription Drug Supply Chain," April 25, 2013, <http://www.fda.gov/NewsEvents/Testimony/ucm349186.htm>.

chain stakeholders participate in the system and if all legitimate products have a way to be identified and tracked as they are distributed from the point of manufacture.

Many Members of the current Congress have been trying, as had their predecessors, to craft legislation that could help (1) keep counterfeit, mishandled, and substandard drugs away from patients; (2) maintain clear lines of accountability; (3) use appropriate levels of technology and data management; and (4) avoid unintentional adverse effects on patients, industry, communication systems, and relationships of all with each other and the states and FDA. Current<sup>62</sup> congressional attention is on H.R. 3204, the Drug Quality and Security Act, the text of which was released as an agreement by majority and majority leadership of the Senate Committee on Health, Education, Labor, and Pensions and the House Committee on Energy and Commerce on September 25, 2013. Title II is the proposed Drug Supply Chain Security Act. The House passed H.R. 3204 on September 28, 2013. The bill now awaits Senate action.

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<sup>62</sup> Earlier in the 113<sup>th</sup> Congress, the House Committee on Energy and Commerce and the full House passed H.R. 1919, the Safeguarding America's Pharmaceutical's Act, and the Senate Committee on Health, Education, Labor, and Pensions reported S. 959, the Pharmaceutical Quality, Security, and Accountability Act.